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Measurement and Correlation of Solubility of Some Synthetic Dihydropyrimidines in Dimethylsulfoxideat (298.15 to 318.15) K

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Abstract

The solubility (x) of some derivatives of dihydropyrimidines in dimethylsulfoxide was measured by a gravimetry method from (298.15 to 318.15) K under atmospheric pressure and some thermodynamic parameters such as Gibbs free energy, enthalpy and entropy of solutions have been evaluated. The solubility is found to increase with temperature.

Keywords: Dihydropyrimidines; DMSO; Gravimetry; Solubility; Thermodynamic parameters.

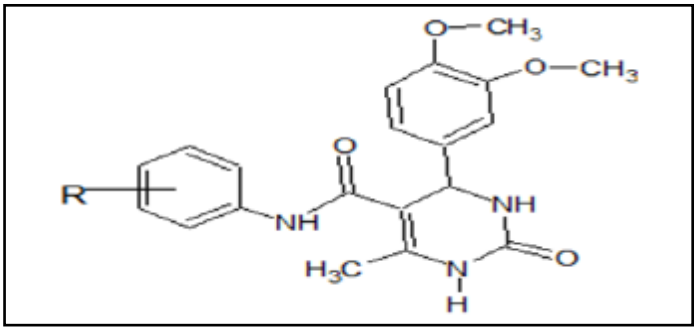
1. Introduction

Dihydropyrimidines are an important class of compounds, which is becoming increasingly important due to their therapeutic and pharmacological properties(1). They have emerged as the integral backbones of several calcium channel blockers, antihypertensive agents, and alpha-1α-antagonists(2). Recently,Sinder et al.(3)shows several isolated marine alkaloids with interesting biological activities were also found to contain the dihydropyrimidinone-5-carboxylate core. Rama Rao et al.(4) have shown that the most notably among them are the batzelladine alkaloids, which have been found to be potent human immunodeficiency virus (HIV) gp-120-CD4 inhibitors.Due to their various applications, it will be interesting to study their solubilities in various solvents which may help their uses in other fields also. Thus, in the present article, we have studied the solubilities of dihydro pyrimidines in DMSOfrom (298.15 to 318.15) K at atmospheric pressure.

2. Experimental Section

2.1. Materials: The synthesized dihydropyrimidines derivatives were recrystallized in ethanol and their purity was checked by elemental analysis, IR, NMR and mole spectral data.Fig. 1 shows the general structure of these compounds. The melting temperature of all the synthesized compounds was determined by DSC.

Figure 1.General Structure of Dihydropyrimidines derivative



Where R =

RVG -1: 4- $OCH_3C_6H_4$

RVG -2: 4- $CH_3C_6H_4$

RVG -3: 4- ClC_6H_4

RVG -4: 4- $CH_3C_6H_4$

RVG -5: 2- $OCH_3C_6H_4$

RVG -6: 4- FC_6H_4

RVG -7: 3- ClC_6H_4

RVG -8: 2, 5 di ClC_6H_4

RVG -9: 3, 4 di ClC_6H_4

RVG -10: 3-Cl, 4-F C_6H_3

The choice of solvent depends upon solubility and relative permeability. DMSO waspurified by fractional distillation[5] and itspurity was checked by SHIMADZU GC-MS (Model No QP-2010) and was found to be greater than 99.75 %.

2.2. Solubility Measurement: The solubilities were measured by a gravimetric method which was previously shown by Zhu, M (2001). For each measurement, an excess mole of compound was added to a known mole of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After, at least 3 h (the temperature of the water bath approached constant value, then the actual value of the temperature was recorded), the stirring was stopped and the solution was kept still for 2 h. A portion of this solution was filtered and by a preheated injector, 2 ml of this clear solution was taken in another weighted measuring vial (m_0). The vial was quickly and tightly closed and weighted (m_1) to determine the mole of the sample (m_1- m_0). Then, the vial was covered with a piece of filter paper to prevent dust contamination. After the solvent in the vial had completely evaporated at room temperature, the vial was dried and reweighed (m_2) to determine the mole of the constant residue solid (m_2- m_0). All the molees were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. Thus, the concentration of the solid sample in the solution, mole fraction, x, could be determined from eq1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

where M_1 is the molar mole of compound and M_2 is the molar mole of the solvent.

At each temperature, the measurement was repeated three times and an average value is given in Table 1.

Table 1. Observed Mole fraction Solubilities (*x*), Calculated Mole fraction Solubilities (x_{ci}) andrelative deviation (*RD*) of Dihydro pyrimidines in DMSO

T/K	*x*	x_{ci}	100 RD
RVG-1			
298.15	2.2628	2.2440	-0.2374
303.15	2.3440	2.3216	-0.1593
308.15	2.4262	2.4019	-0.2888
313.15	2.5095	2.4850	-0.2842
318.15	2.5937	2.5709	-0.2599
RVG-2			
298.15	2.2130	2.2481	0.3947

303.15	2.2867	2.2958	0.0866
308.15	2.2805	2.3445	0.7147
313.15	2.3589	2.3943	0.3789
318.15	2.4174	2.4451	0.2880
RVG-3			
298.15	2.1397	2.1818	0.4878
303.15	2.2548	2.2685	0.1418
308.15	2.2699	2.3587	0.9965
313.15	2.3984	2.4525	0.5799
318.15	2.5185	2.5500	0.3203
RVG-4			
298.15	2.5097	2.4869	-0.2660
303.15	2.5813	2.5460	-0.3944
308.15	2.6329	2.6066	-0.2943
313.15	2.6902	2.6685	-0.2417
318.15	2.7675	2.7320	-0.3784
RVG-5			
298.15	2.1226	2.1778	-0.6491
303.15	2.2540	2.2498	-0.0671
308.15	2.3853	2.3241	-0.7143
313.15	2.4012	2.4008	-0.0220
318.15	2.4171	2.4801	-0.6739

T/K	**$10^2 x$**	**$10^2 x_{ci}$**	**100 RD**
RVG-6			
298.15	2.0230	2.0159	-0.1072
303.15	2.1122	2.0784	-0.4361
308.15	2.2013	2.1427	-0.7253

313.15	2.2285	2.2091	-0.2485
318.15	2.2957	2.2775	-0.2293
RVG-7			
298.15	1.9252	1.9241	-0.0331
303.15	2.0087	1.9797	-0.3905
308.15	2.0422	2.0369	-0.0846
313.15	2.1093	2.0958	-0.1846
318.15	2.1694	2.1563	-0.1759
RVG-8			
298.15	2.0242	2.0346	0.1137
303.15	2.0901	2.1060	0.1778
308.15	2.1661	2.1799	0.1486
313.15	2.2394	2.2564	0.1819
318.15	2.3227	2.3356	0.1298
RVG-9			
298.15	2.1708	2.1619	-0.1256
303.15	2.2611	2.2378	-0.2915
308.15	2.3214	2.3163	-0.0759
313.15	2.4119	2.3976	-0.1777
318.15	2.4986	2.4818	-0.2010
RVG-10			
298.15	2.2280	2.2455	0.1868
303.15	2.2978	2.3185	0.2192
308.15	2.3782	2.3938	0.1571
313.15	2.4663	2.4717	0.0411
318.15	2.5123	2.5520	0.4079

3. Results and Discussion:

The mole fraction solubilities x of dihydropyrimidines derivatives in DMSOat different temperatures (298.15 to 318.15 K) are summarized in Tables 1. It is observed that solubility increases linearly with increase in temperature.

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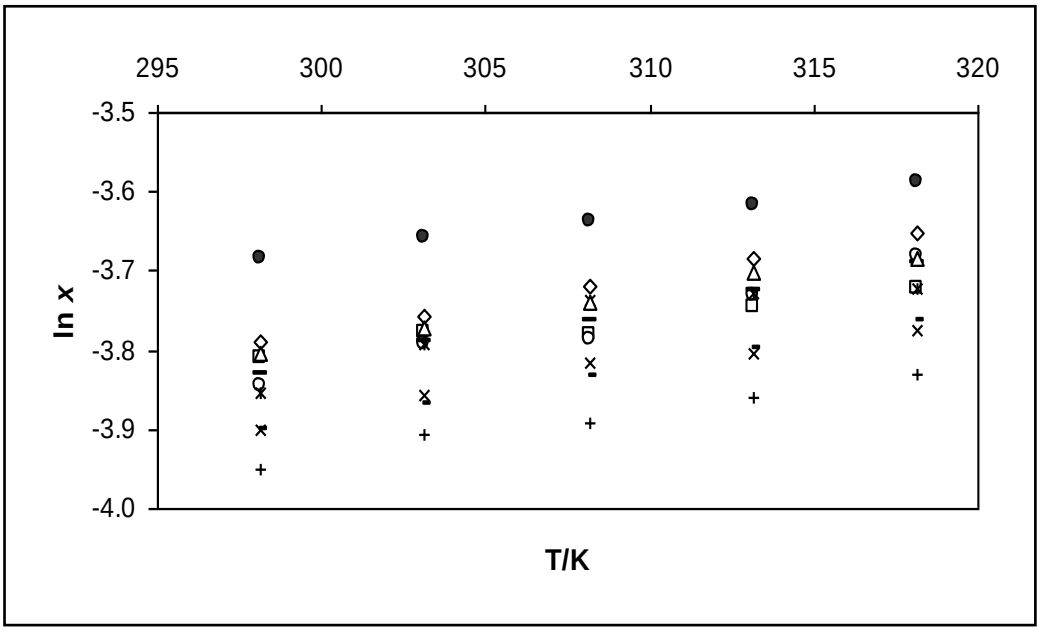
The mole fraction solubility x of pyrimidines was correlated as a function of temperature. The temperature dependence of pyrimidines solubility in solvents is described by the modified Apelblat equation shown by Apelblat A. et al. (1999) and Gao, J. et al. (2007).

$$ln\ x = A + B\ (T/K) \quad (2)$$

where xis the mole fraction solubility of dihydropyrimidines; T is the absolute temperature and A and B are the parameters. Figure 2 shows the plot of ln x versus T. The values of these parameters are given in Table2. The calculated solubilities $x_{ci}$are also reported in Table 1.

Figure 2. Solubility x of Dihydropyrimidines as a function of temperature in DMSO. RVG -1, ◊; RVG -2, □; RVG -3, o; RVG -4, ● ; RVG -5, χ; RVG -6, X; RVG -7, +; RVG -8,–; RVG -9, ▬; RVG -10, Δ



Further, relative average deviations (ARD) and root-mean-squaredeviations (RMSD), calculated by equations (3) and (4) are listed in Table 2.

$$ARD = \frac{1}{N}\sum_{i}^{N}\frac{x_i - x_{ci}}{x_i} \quad (3)$$

$$RMSD = \left[\sum_{i=1}^{N}\frac{(x_{ci} - x_i)^2}{N-1}\right]^{1/2} \quad (4)$$

where N is the number of experimental points and x_{ci} is the solubility calculated by equation 2.

Table 2. Constants A and B of eq (2), Relative Average Deviations (ARD), and Root Mean Square Deviation (RMSD) of Dihydropyrimidines in DMSO

Compounds	*A*	*B*	10^7 RMSD	100 ARD
RVG-1	-5.82	0.0068	0.17	-0.2459
RVG-2	-5.05	0.0042	0.59	0.3726
RVG-3	-6.15	0.0078	1.10	0.5053
RVG-4	-5.09	0.0047	0.33	-0.3150
RVG-5	-5.76	0.0065	0.86	0.1039

RVG-6	-5.72	0.0061	0.42	-0.3493
RVG-7	-5.65	0.0057	0.09	-0.1737
RVG-8	-5.95	0.0069	0.08	0.1504
RVG-9	-5.89	0.0069	0.09	-0.1743
RVG-10	-5.70	0.0064	0.20	0.2024

The relative deviations (RD) between the experimental and calculated values of solubilities are also calculated by equation 5 and are given in Table 1.

$$Relative\ Deviation\ = \left(\frac{x - x_{ci}}{x} \right) \tag{5}$$

The heat of solution (ΔH_{sol}) was calculated by modified van't Hoff equationas previously reported by Krug et al. (1976) and Kalsi P. (2004).

$$\frac{\partial \ln x}{\partial \left(1/T - 1/T_{hm} \right)_P} = -\frac{\Delta H_{sol}}{R} \tag{6}$$

where T is the experimental temperature and R is gas constant. $T_{hm}$is the mean harmonic temperature which is given as:

$$T_{hm} = \frac{n}{\sum_{i}^{n} \left(1/T \right)} \tag{7}$$

where n is the number of experimental temperatures(El-Bindary et al. 2003). In the present case, theT_{hm}value obtained is only 308 K. The slope of the plot of ln *x* versus (*1/T*-1/308) gives the value of ΔH_{sol}.

The Gibbs energy change for the solubility process was then evaluated from the following relation[8]

$$\Delta G_{sol} = -RT.\ intercept \tag{8}$$

Using these evaluated ΔH_{sol} and ΔG_{sol} values, the entropy of solution ΔS_{sol} were obtained from equation[8, 9]

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \tag{9}$$

All these thermodynamic parameters are given in Table 3.

Table 3. Thermodynamic parameters of dissolution of Dihydropyrimidines in DMSO

Compounds	ΔG/kJ.mol^{-1}	ΔH/kJ.mol^{-1}	ΔS/J.mol^{-1}.K^{-1}
RVG-1	2.27	1.28	-3.22
RVG-2	2.30	0.78	-4.93
RVG-3	2.30	1.46	-2.72
RVG-4	2.22	0.89	-4.32
RVG-5	2.30	1.22	-3.49
RVG-6	2.34	1.15	-3.84

RVG-7	2.38	1.07	-4.24
RVG-8	2.34	1.29	-3.40
RVG-9	2.30	1.30	-3.24
RVG-10	2.28	1.20	-3.50

It is evident from Table 3 that for all the compounds ΔH_{sol} and ΔG_{sol} values in both the solvents are positive whereas ΔS_{sol} values are negative. When stronger bonds are broken and weaker bonds are formed, energy is consumed. So, ΔH_{sol} becomes positive.[9] This indicates endothermic dissolution of compounds where the enthalpy term contributes to an unfavorable positive value of ΔG_{sol}. Thus, positive value of ΔG_{sol} indicates that the dissolution process is not spontaneous.[9, 10] The negative value of entropy indicates increased order due to solvation process.

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